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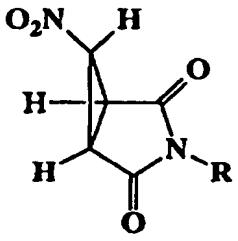
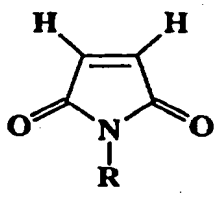
(54) Title: PROCESS FOR PREPARING DIOXOAZABICYCLOHEXANES

(57) Abstract

A process for preparing a compound of formula (I) wherein R is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or benzyl, and wherein the phenyl moiety of said benzyl group is optionally substituted by one or more substituents each independently selected from halo, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino and trifluoromethyl, which comprises adding a solution comprising a compound of formula (II), a halonitromethane and an organic solvent selected from acetone, dimethylformamide, dimethylacetamide, acetonitrile, dimethylsulfoxide, N-methylpyrrolidinone and dimethoxyethane. In formula (II), wherein R is as defined above, to a mixture comprising a base and an organic solvent, said organic solvent being as defined above and the said base being selected from potassium carbonate, sodium carbonate, cesium carbonate, trisodium phosphate, and potassium fluoride, so that a compound of formula (I) is produced, any excess base being eliminated from the reaction mixture prior to recovery of the product (I).



(I)



(II)

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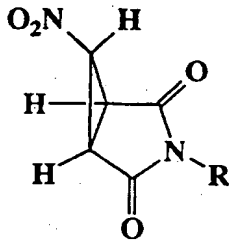
Process for preparing dioxoazabicyclohexanes.

This invention relates to a process for preparing an exo-compound of the formula (I):-



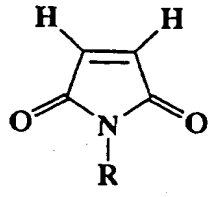
--- (I)

wherein R is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or benzyl, and wherein the phenyl moiety of said benzyl group is optionally substituted by one or more substituents each independently selected from halo, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino and trifluoromethyl.

Halo means fluoro, chloro, bromo or iodo.

The compounds (I) are useful as synthetic intermediates in the manufacture of the antibiotics of EP-B-0413455 as explained in WO-A-93/18001.

International patent application publication no. WO-A-93/18001 describes a process for preparing a compound of the formula (I) by reaction of a compound of the formula (II):-



--- (II)

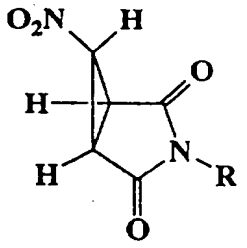
with a halonitromethane in the presence of a base, R being as defined for formula (I).

Example 1 of that application describes the preparation of 1α, 5α, 6α-3-benzyl-6-nitro-2,4-dioxo-3-azabicyclo [3.1.0]hexane by adding the base DBU (1,8-diazabicyclo [5.4.0] undec-7-ene) in toluene dropwise to a mixture of N-benzylmaleimide and bromonitromethane in toluene. However the yield of the end product isolated was only 17%. In terms of grams of activity, the yield would have been less than 17%.

WO-A-95/19361 describes the use of 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine (DMTHP) as the base in that process and the isolated yield was 26.7% (less in terms of grams of activity).

We have now found that if certain specific bases and solvents are used, if the order of addition of the reactants is reversed [i.e., if the halonitromethane and maleimide (II)are added to the base in the solvent], and if any excess base is eliminated from the reaction mixture before recovery of the product (I), then very significant improvements in the yield of (I) are obtained.

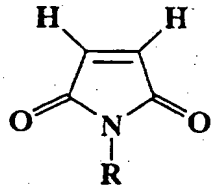
Thus the present invention provides a process for preparing a compound of the formula (I):-



--- (I)

wherein R is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or benzyl, and wherein the phenyl moiety of said benzyl group is optionally substituted by one or more substituents each independently selected from halo, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino and trifluoromethyl,

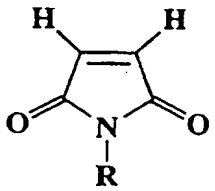
which comprises adding a solution comprising a compound of the formula (II), a halonitromethane and an organic solvent selected from acetone, dimethylformamide, dimethylacetamide, acetonitrile, dimethylsulfoxide, N-methylpyrrolidinone and dimethoxyethane,



--- (II)

wherein R is as defined above,
to a mixture comprising a base and an organic solvent, said organic solvent being as defined above and said base being selected from potassium carbonate, sodium carbonate, cesium carbonate, trisodium phosphate, and potassium fluoride, so that a compound of the formula (I) is produced, any excess base being eliminated from the reaction mixture prior to recovery of the product (I).

In one aspect, the process comprises adding a solution of a compound of the formula (II) in a mixture of a halonitromethane and an organic solvent, said organic solvent being selected from acetone, dimethylformamide, dimethylacetamide, acetonitrile, dimethylsulfoxide, N-methylpyrrolidone and dimethoxyethane,



(II)

wherein R is defined for formula (I),
to a mixture of a base in an organic solvent, said organic solvent being as defined above and the base being selected from potassium carbonate, sodium carbonate, cesium carbonate, trisodium phosphate, and potassium fluoride, so that a compound of the formula (I) is produced, any excess base being eliminated from the reaction mixture prior to recovery of the product (I).

Preferably R is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or benzyl, the phenyl moiety of the benzyl group being optionally substituted by 1 or 2 substituents as defined above.

Preferably, R is C_1-C_6 alkyl or benzyl.

Most preferably, R is benzyl.

Preferably, the halonitromethane is chloronitromethane or bromonitromethane, most preferably bromonitromethane.

Bromonitromethane is conveniently purchased as a solution in a stabilizing amount of an inert organic solvent, such as toluene, and preferably as a solution in from 25 to 50%w/w toluene. The presence of the inert solvent, such as toluene, does not significantly affect the yield of the compound (I), so that the solution of bromonitromethane in the inert solvent can be used as such in the process of the invention.

Mixtures of the stated organic solvents, and of the bases, may also be used.

Preferably, the ratio of the volume of the organic solvent in the mixture of the base and the organic solvent : the volume of the organic solvent in the solution of the compound (II) and bromonitromethane is from approximately 1:1 to 7:1, preferably from 1:1 to 4:1.

Preferably, the compound (II) and the halonitromethane are used in a molar ratio of from 1:1 to 1:1.25. Most preferably, the molar ratio is about 1:1.

Typically, the solution of the compound (II) in the mixture of the halonitromethane and organic solvent is slowly added to the base/solvent mixture, e.g. over a period of from 30 minutes to 4 hours.

Preferably, the mixture of the base and the organic solvent contains up to 5%, more preferably 1-3%, by volume water based on the total volume of the organic solvent(s).

In one preferred aspect, the organic solvent is dimethylformamide and the base is potassium carbonate.

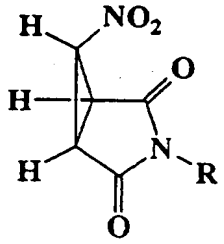
In another preferred aspect, the organic solvent is dimethylsulfoxide and the base is potassium carbonate.

The process is preferably carried out at a temperature of from 5 to 50°C, preferably from 20°C to 30°C, and most preferably at ambient temperature.

Preferably, any excess base is eliminated from the reaction mixture by filtration, or by neutralisation with an acid. Most preferably, any excess base is removed by neutralisation with acetic or dilute hydrochloric acid.

Preferably, the particle size of the base is less than 75, more preferably less than 45, microns.

Whilst the process as described produces the exo compound (I) in good to excellent yield it is believed that a portion of (I) is produced via the epimerisation of the endo isomer (III), which is also produced in this process:-



--- (III)

R is as defined for formula (I).

The following Examples illustrate the high yields obtainable by the process of the present invention :gA=grams of activity.

Example 1

1α, 5α, 6α-3-Benzyl-6-nitro-2,4-dioxo-3-azabicyclo[3.1.0]hexane.

To a stirred slurry of potassium carbonate (7.5g;0.054 mole) in acetone (40 ml) and water (1 ml) at ambient temperature was added dropwise, over a period of about 2 hours, a solution of bromonitromethane (5 g - 4.48gA, 0.032 mole) and N-benzylmaleimide (5 g; 0.026 mole) in acetone (40 ml).

When reaction was complete (in situ yield 61%), powdered molecular sieves (10 g) were added and the solvent exchanged with toluene by constant volume distillation. The resulting slurry was filtered to remove unreacted potassium carbonate/sieves/tar and the filter cake washed with toluene.

The combined toluene filtrates were washed with dilute hydrochloric acid (2M), then concentrated under reduced pressure to approximately 20 ml then cooled to 0-5°C. The desired product was subsequently isolated by filtration and dried in vacuo to yield the title compound (3.03gA, 46%) as a white to pale yellow crystalline solid, m.p. 115°C. NMR ($CDCl_3$): δ 3.34 (s,2H), 4.46 (s,1H), 4.53 (s, 2H), 7.3 (s, 5H).

Example 2

1α, 5α, 6α-3-Benzyl-6-nitro-2,4-dioxo-3-azabicyclo [3.1.0]hexane.

To a stirred slurry of potassium carbonate (7.5 g, 0.054 mole) in dimethylformamide (40 ml) and water (1 ml) at ambient temperature was added dropwise, over a period of about 2 hours, a solution of bromonitromethane (5 g - 4.48gA, 0.032 mole) and N-benzylmaleimide (5 g; 0.026 mole) in dimethylformamide (40 ml).

When the reaction was complete (in situ 72%), the excess potassium carbonate was neutralised by the addition of acetic acid (4.68 g, 0.078 mole) and then water (160 ml) was added. The resulting precipitate was isolated by filtration and dried in vacuo to yield the title compound (4.2 gA, 66%) as an

off-white/light brown solid, m.p. 114°C. NMR ($CDCl_3$) :δ 3.34 (s, 2H), 4.46 (s, 1H), 4.53 (s, 2H), 7.3 (s, 5H).

Example 3

1α, 5α, 6α-3-Benzyl-6-nitro-2,4-dioxo-3-azabicyclo [3.1.0] hexane.

To a stirred slurry of potassium carbonate (7.5 g, 0.054 mole) in dimethylformamide (40 ml) and water (1 ml) at ambient temperature was added dropwise, over a period of about 2 hours, a solution of bromonitromethane (5 g - 4.48gA, 0.032 mole) and N-benzylmaleimide (5 g; 0.026 mole) in dimethylformamide (40 ml).

When the reaction was complete, the excess potassium carbonate was removed by filtration and then water (160 ml) was added.. The resulting precipitate was isolated by filtration and dried in vacuo to yield the title compound (3.5gA, 54%) as a light brown solid, m.p. 116-117°C. NMR ($CDCl_3$) : δ 3.34 (s, 2H), 4.46 (s, 1H), 4.53 (s, 2H), 7.3 (s, 5H).

Examples 4-17

1α, 5α, 6α-3-Benzyl-6-nitro-2,4-dioxo-3-azabicyclo [3.1.0] hexane was prepared similarly to the procedure of Example 1 using N-benzylmaleimide and bromonitromethane in the presence of water and using the stated base/solvent combinations. Although the title compound was not actually isolated in these Examples, the in situ yields of it were measured using hplc following the end of reaction. The isolated yields will be about 5 -15% lower than the in situ yields.

Example No	Base	Solvent	Molar Ratio NBM:BNM	Water (by vol. based on the total vol.of the organic solvent)	In Situ Yield
4	Pot.Carbonate	Acetonitrile	1:1.25	1.25%	60%
5	Pot.Carbonate	DMSO	1:1.25	1.25%	69%
6	Pot.Carbonate	DMF	1:1	1.25%	74%
7	Pot. Carbonate	DMF	1:1	1.25%	75%
8	Pot.Carbonate	DMAC	1:1:25	1.25%	66%
9	Pot.Carbonate	NMP	1:1.25	1.25%	68%
10	Pot.Carbonate	DME	1:1.25	1.25%	54%
11	Cesium Carbonate	Acetone	1:1.25	0.5%	63%
12	Cesium Carbonate	DMF	1:1.25	1.25%	78%
13	Sodium Carbonate	DMF	1:1.25	1.25%	61%
14	Trisodium Phosphate	DMF	1:1	1.25%	58%
15	Pot. Fluoride	Acetonitrile	1:1.25	1.25%	47%
16	Pot. Fluoride	Acetone	1:1.25	1%	54%
17	Pot. Fluoride	DMF	1:1.25	1.25%	68%

Hplc Method:

Column: Waters "Novapak" C18 15 cm x 3.9 mm i.d.

Mobile Phase: 60:40 0.02 M aqueous sodium dihydrogen phosphate:acetonitrile.

Flow rate: 1.0 ml. min $^{-1}$l.

UV detection at 220 nm

Approx. retention times:

N-Benzylmaleimide 3.47 minutes.

Bromonitromethane 1.88 minutes.

Title compound 4.59 minutes.

DMSO = Dimethylsulfoxide. DMF = dimethylformamide.

DMAC = dimethylacetamide. NMP = N-methylpyrrolidinone.

DME = dimethoxyethane.

NBM = N-benzylmaleimide. BNM = Bromonitromethane. Pot. = potassium.

Example 18

To a stirred slurry of potassium carbonate (30g, 0.2136 mole) in DMF (140 ml) and water (4 ml) at ambient temperature was added dropwise, over a period of about 2 hours, a solution of bromonitromethane [36.2g of a 47.5% w/w solution in toluene (about 20 ml), equivalent to 17.19 gA, 0.123 mole] and N-benzylmaleimide (20g, 0.1068 mole) in DMF (20 ml). When the reaction was complete (in situ yield 75%) the excess potassium carbonate was neutralised via the addition of acetic acid (19.4 ml, 20.35 g, 0.34 mole) and then water (160 ml) was added.

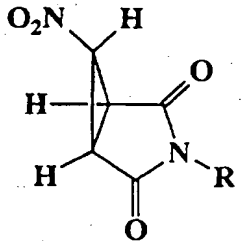
The resulting precipitate was isolated by filtration, washed with water (3 x 40 ml) and then isopropanol (3 x 20 ml) to give the title compound (17.54 gA, 66.7%).

NMR ($CDCl_3$) : δ 3.34 (s,2H), 4.46 (s,1H), 4.53 (s,2H), 7.3 (s,5H).

In the above Examples, the particle size of the bases used was less than 75 microns.

CLAIMS

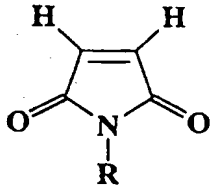
1. A process for preparing a compound of the formula (I):-



--- (I)

wherein R is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or benzyl, and wherein the phenyl moiety of said benzyl group is optionally substituted by one or more substituents each independently selected from halo, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino and trifluoromethyl.

which comprises adding a solution comprising a compound of the formula (II), a halonitromethane and an organic solvent selected from acetone, dimethylformamide, dimethylacetamide, acetonitrile, dimethylsulfoxide, N-methylpyrrolidinone and dimethoxyethane,



--- (II)

wherein R is as defined above,

to a mixture comprising a base and an organic solvent, said organic solvent being as defined above and said base being selected from potassium carbonate, sodium carbonate, cesium carbonate, trisodium phosphate, and potassium fluoride, so that a compound of the formula (I) is produced, any excess base being eliminated from the reaction mixture prior to recovery of the product (I).

2. A process according to claim 1, which comprises adding a solution of a compound of the formula (II) as defined in claim 1 in a mixture of a halonitromethane and an organic solvent, said organic solvent being selected from acetone, dimethylformamide, dimethylacetamide, acetonitrile,

dimethylsulfoxide, N-methylpyrrolidone and dimethoxyethan , to a mixture of a base in an organic solvent, said organic solvent being as defined above and the base being selected from potassium carbonate, sodium carbonate, cesium carbonate, trisodium phosphate, and potassium fluoride, so that a compound of the formula (I) is produced, any excess base being eliminated from the reaction mixture prior to recovery of the product (I).

3. A process according to claim 1 or 2, wherein R is C_1-C_6 alkyl or benzyl..

4. A process according to claim 3, wherein R is benzyl.

5. A process according to any one of the preceding claims, wherein the halonitromethane is chloronitromethane or bromonitromethane.

6. A process according to claim 5, wherein the halonitromethane is bromonitromethane.

7 A process according to claim 6, where the bromonitromethane is used as a solution in a stabilising amount of an inert organic solvent.

8. A process according to claim 7, wherein the bromonitromethane is used as a solution containing from 25 to 50% w/w toluene.

9. A process according to any one of the preceding claims, wherein the compound (II) and the halonitromethane are used in a molar ratio of from 1:1 to 1:1.25.

10. A process according to claim 8, wherein the molar ratio is about 1:1.

11. A process according to any one of the preceding claims, wherein the mixture of the base and the organic solvent contains up to 5% by volume water based on the total volume of the organic solvent(s).

12. A process according to claim 10, wherein the mixture contains from 1-3% by volume water.

13. A process according to any one of the preceding claims, wherein the organic solvent is dimethylformamide and the base is potassium carbonate.

14. A process according to any one of claims 1 to 12, wherein the organic solvent is dimethylsulfoxide and the base is potassium carbonate.

15. A process according to any one of the preceding claims, which is carried out at a temperature of from 5 to 50°C.

16. A process according to claim 14, which is carried out at a temperature of from 20°C to 30°C.

17. A process as claimed in claim 16, which is carried out at ambient temperature.

18. A process according to any one of the preceding claims, wherein any excess base is eliminated from the reaction mixture either by filtration, or by neutralisation with an acid.

19. A process according to claim 18, wherein any excess base is removed by neutralisation with acetic or dilute hydrochloric acid.

20. A process according to any one of the preceding claims, wherein the particle size of the base is less than 75 microns.

21. A process according to any one of the preceding claims wherein the solution of the compound (II) in the mixture of the halonitromethane and organic solvent is slowly added to the base/solvent mixture.

22. A process according to any one of the preceding claims wherein the ratio of the volume of the organic solvent in the mixture of the base and organic solvent : the volume of the organic solvent in the solution of compound (II) and bromonitromethane is from approximately 1:1 to 7:1.

INTERNATIONAL SEARCH REPORT

Int ɔnal Application No
PCT/EP 96/04782

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 19361 A (PFIZER INC.) 20 July 1995 cited in the application see example 1 ---	1
A	WO 93 18001 A (PFIZER INC.) 16 September 1993 cited in the application see example 1 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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24 January 1997	05. 02. 97

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Information on patent family members

Inte onal Application No
PCT/EP 96/04782

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